PALM INTRANET

Day : Wednesday
Date: 10/4/2006
Time: 13:00:46

Inventor Information for 60/447558

Inventor Name	City	State/Country
MARQUIS, ROBERT W.	COLLEGEVILLE	PENNSYLVANIA

Appln Info | Contents | Petition Info | Atty/Agent Info | Continuity/Reexam | Foreign Data | Invento

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PCT / [ ] / [ ] Search **or PG PUBS #** [ ] Search

Attorney Docket # [ ] Search

Bar Code # [ ] Search

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     FILE 'CAPLUS' ENTERED AT 14:10:43 ON 04 OCT 2006
L1             0 S US10772817/PN
L2             0 S US10/772817/PN
L3             0 S MARQUIS AND QUINOLINE-6-CARBOXYLIC
L4            95 S QUINOLINE-6-CARBOXYLIC
L5             1 S L4 AND AZEPAN-4-YL
L6             1 S US 2004-192674/PN
L7             4 S 350796-38-2/RN OR 350796-41-7/RN OR 764650-55-7/RN
L8             4 DUP REM L7 (0 DUPLICATES REMOVED)

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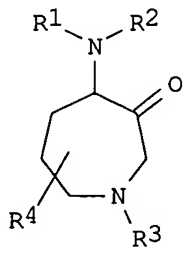
L6 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:803931 CAPLUS
DOCUMENT NUMBER: 141:295878
TITLE: Preparation of aminoazepanones as Cathepsin L inhibitors
INVENTOR(S): Marquis, Robert W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004192674	A1	20040930	US 2004-772817		20040205 <--
PRIORITY APPLN. INFO.:			US 2003-447558P	P	20030214

OTHER SOURCE(S): MARPAT 141:295878
GI



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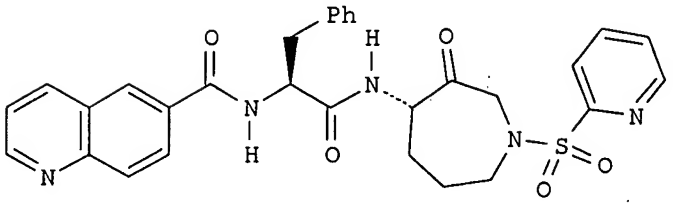

II

AB The title compds. I [R1 = substituted aminoalkylcarbonyl; R2 = H, alkyl, arylalkyl, etc.; R3 = H, alkyl, cycloalkyl, arylalkyl, etc.; R4 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts are prepared and disclosed as inhibitors of Cathepsin L. Thus, e.g., II was prepared in a multistep synthesis employing N-Boc-phenylalanine. Consequently they are useful for preventing or treating diseases in which cathepsin L is implicated, such as rheumatoid arthritis or inhibition of pos. selection of CD4 + T-cells by cortical thymic epithelial cells.

IT CD4-positive T cell
(inhibition of pos. selection; preparation of aminoazepanones as inhibitors of Cathepsin L)

IT Antirheumatic agents
Rheumatoid arthritis
(preparation of aminoazepanones as inhibitors of Cathepsin L)

IT 350796-38-2P 350796-41-7P 764650-55-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES

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      (Uses)
         (drug candidate; preparation of aminoazepanones as inhibitors of Cathepsin
         L)
IT    60616-82-2, Cathepsin L
      RL: BSU (Biological study, unclassified); BIOL (Biological study)
         (inhibition of; preparation of aminoazepanones as inhibitors of Cathepsin L)
IT    150989-59-6P, 8-Oxa-3-azabicyclo[5.1.0]octane-3-carboxylic acid benzyl
      ester   150989-61-0P, 4-Amino-3-hydroxyazepane-1-carboxylic acid benzyl
      ester   150989-62-1P, 2,3,4,7-Tetrahydroazepine-1-carboxylic acid benzyl
      ester   281219-32-7P   281219-33-8P, 4-Azido-3-hydroxyazepane-1-carboxylic
      acid benzyl ester   369593-24-8P   369593-25-9P   764650-56-8P
      764650-57-9P
      RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
      (Reactant or reagent)
         (intermediate; preparation of aminoazepanones as inhibitors of Cathepsin L)
IT    1119-51-3, 5-Bromo-1-pentene   5041-33-8   10349-57-2,
      Quinoline-6-carboxylic acid   13734-34-4   58438-04-3   66715-65-9,
      Pyridin-2-sulfonyl chloride
      RL: RCT (Reactant); RACT (Reactant or reagent)
         (preparation of aminoazepanones as inhibitors of Cathepsin L)
RN    350796-38-2P
RN    350796-41-7P
RN    764650-55-7P
RN    60616-82-2
RN    150989-59-6P
RN    150989-61-0P
RN    150989-62-1P
RN    281219-32-7P
RN    281219-33-8P
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RN    369593-25-9P
RN    764650-56-8P
RN    764650-57-9P
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RN    10349-57-2
RN    13734-34-4
RN    58438-04-3
RN    66715-65-9


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             4 350796-41-7
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             1 764650-55-7
             0 764650-55-7D
             1 764650-55-7/RN
                 (764650-55-7 (NOTL) 764650-55-7D )
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PROCESSING COMPLETED FOR L7
L8           4 DUP REM L7 (0 DUPLICATES REMOVED)

=> d ibib abs hitstr 1-4

L8   ANSWER 1 OF 4   CAPLUS   COPYRIGHT 2006 ACS on STN
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ACCESSION NUMBER: 2004:803931 CAPLUS
DOCUMENT NUMBER: 141:295878
TITLE: Preparation of aminoazepanones as Cathepsin L inhibitors
INVENTOR(S): Marquis, Robert W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004192674	A1	20040930	US 2004-772817		20040205
PRIORITY APPLN. INFO.:			US 2003-447558P	P	20030214

OTHER SOURCE(S): MARPAT 141:295878
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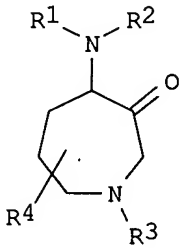

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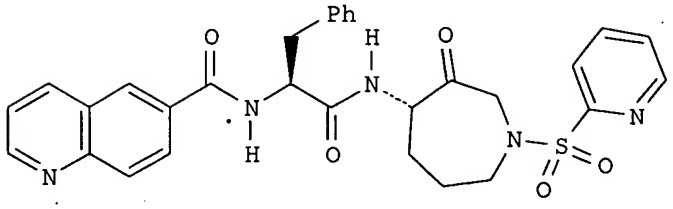


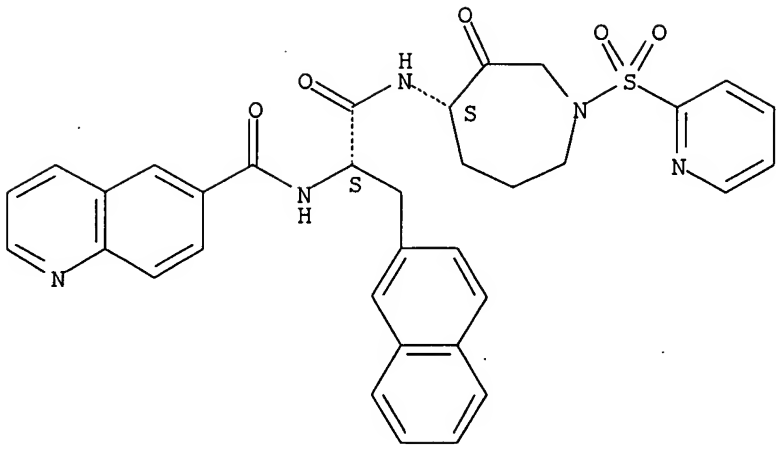
II

AB The title compds. I [R1 = substituted aminoalkylcarbonyl; R2 = H, alkyl, arylalkyl, etc.; R3 = H, alkyl, cycloalkyl, arylalkyl, etc.; R4 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts are prepared and disclosed as inhibitors of Cathepsin L. Thus, e.g., II was prepared in a multistep synthesis employing N-Boc-phenylalanine. Consequently they are useful for preventing or treating diseases in which cathepsin L is implicated, such as rheumatoid arthritis or inhibition of pos. selection of CD4 + T-cells by cortical thymic epithelial cells.

IT **350796-38-2P 350796-41-7P 764650-55-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aminoazepanones as inhibitors of Cathepsin L)

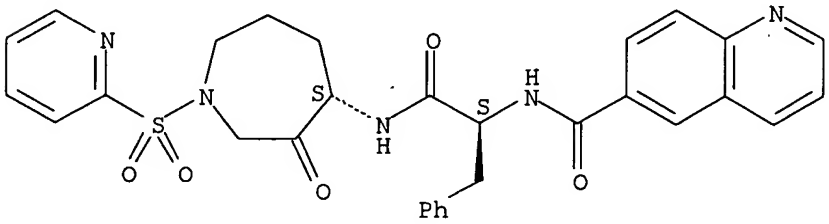
RN 350796-38-2 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



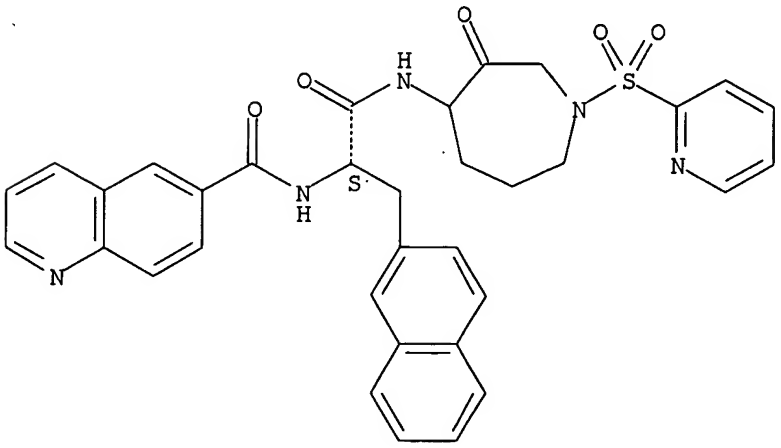
RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 764650-55-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:665404 CAPLUS

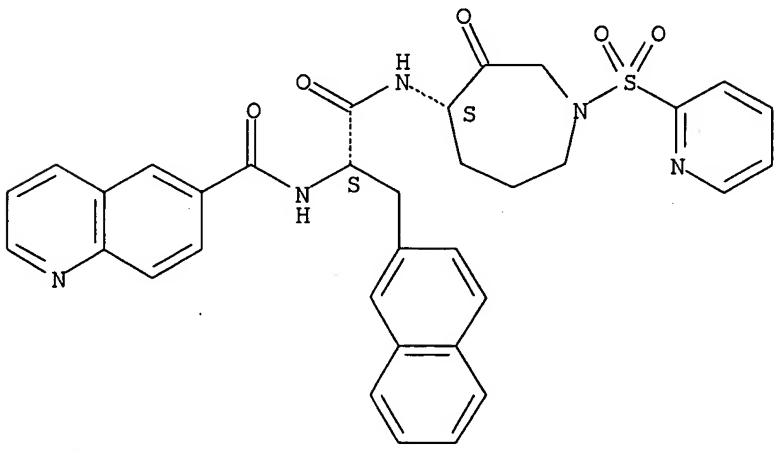
DOCUMENT NUMBER: 141:103796
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro. [Erratum to document cited in CA135:120165]
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Hwang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2003), 278(34), 32484
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In Tables I and II, analogs SB-468430 and SB-468433 were originally reported to contain the quinoline-8-carboxamide moiety. Subsequent resynthesis revealed that in actuality these analogs contain the isomeric quinoline-6-carboxamide moiety. The modified structures are given in revised Tables I and II. Corrected Ki values for cathepsin L and cathepsin K in Table I are also given.

IT **350796-38-2**, SB 468430 **350796-41-7**, SB 468433
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro (Erratum))

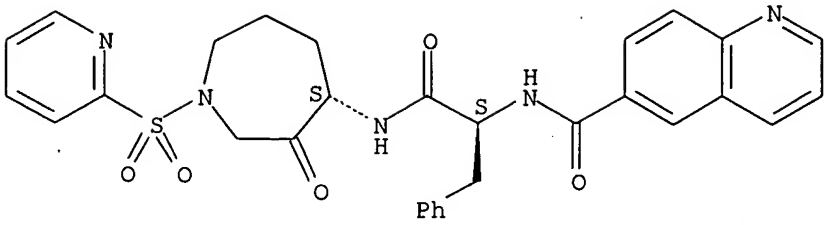
RN 350796-38-2 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L8 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2002:171694 CAPLUS
DOCUMENT NUMBER: 136:232208
TITLE: Preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases
INVENTOR(S): Tew, David G.; Thompson, Scott K.; Veber, Daniel F.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, UK
SOURCE: PCT Int. Appl., 220 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017924	A1	20020307	WO 2001-US27178	20010831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003144175	A1	20030731	US 2001-881334	20010614
AU 2001086983	A5	20020313	AU 2001-86983	20010831
EP 1320370	A1	20030625	EP 2001-966474	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004509083	T2	20040325	JP 2002-522897	20010831

PRIORITY APPLN. INFO.:

US 2000-653815	A2	20000901
US 2001-881334	A2	20010614
US 1998-113636P	P	19981223
US 1999-164581P	P	19991110
WO 1999-US30730	A2	19991221
US 2000-593845	B2	20000614
WO 2001-US27178	W	20010831

OTHER SOURCE(S): MARPAT 136:232208
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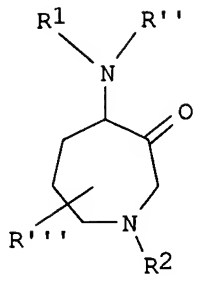

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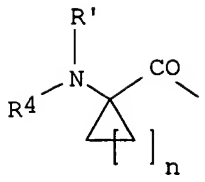


II

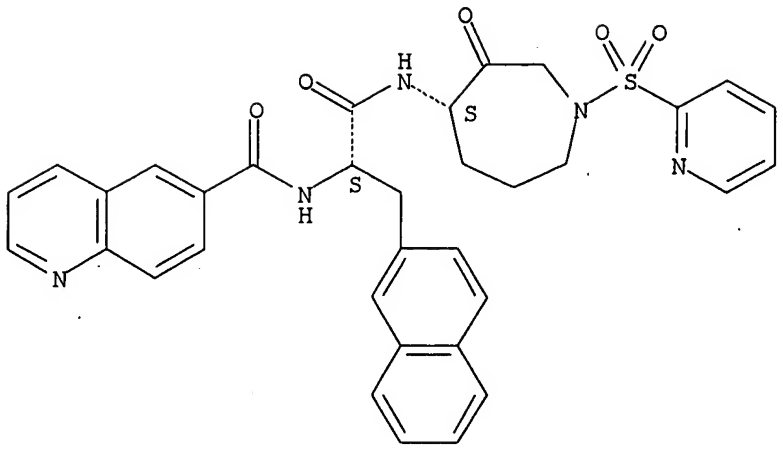
AB The present invention relates to methods of treating parasitic diseases which are mediated by cysteine proteases by administration of 4-aminoazepan-3-one protease inhibitors I (e.g. benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methylbutyl]amide) and pharmaceutically acceptable salts, hydrates and solvates thereof. In particular, the present invention relates to a method of treating malaria by inhibiting the cysteine protease falcipain. Other diseases against which the claimed compds. are effective include trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis. In I: R1 is R4NR'CHR3C(O)-, R5XCHR3C(O)-, R3CH2C(O)-, R4NR'CR''''R3C(O)-, II. R2 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R9C(O)-, R9C(S)-, R9SO2-, R9OC(O)-, R9R11NC(O)-, R9R11NC(S)-, R9(R11)NSO2-, 3-(2-pyridyl)benzylcarbonyl, 2-(3-(2-pyridyl)phenyl)ethyl, R7NR6CHR8Z-, and R9SO2R11NC(O)-. R3 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R3 and R' may be connected to form a pyrrolidine, piperidine or morpholine ring. R4 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R5C(O)-, R5C(S)-, R5SO2-, R5OC(O)-, R5R12NC(O)-, and R5R12NC(S)-. R5 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R6 is H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R7 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R10C(O)-, R10C(S)-, R10SO2-, R10OC(O)-, R10R13NC(O)-, and R10R13NC(S)-. R8 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R9, R10 independently = C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R11, R12, R13, R', R'' independently = H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R''' is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl; R'''' is C1-6alkyl, C3-6cycloalkyl-C0-6alkyl C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. X is CH2, S, and O; Z is C(O) and CH2; n is 1-5. Although the methods of preparation are not claimed, 220 example prepns. are included.

IT **350796-38-2P**, Quinoline-6-carboxylic acid [(1S)-2-(naphthalen-2-yl)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]ethyl]amide **350796-41-7P**, Quinoline-6-carboxylic acid [(1S)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]-2-phenylethyl]amide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases)

RN 350796-38-2 CAPLUS

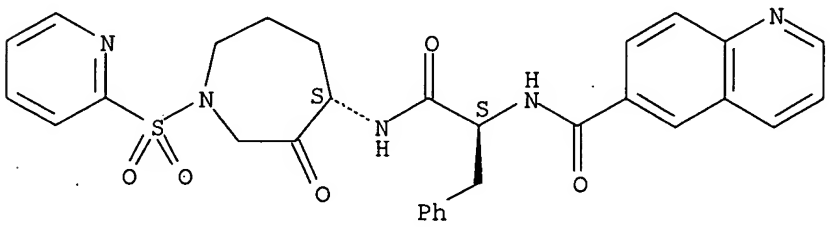
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:318582 CAPLUS
DOCUMENT NUMBER: 135:120165
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Hwang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2001), 276(15), 11507-11511
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cathepsins K and L are related cysteine proteases that have been proposed to play important roles in osteoclast-mediated bone resorption. To further examine the putative role of cathepsin L in bone resorption, we have evaluated selective and potent inhibitors of human cathepsin L and cathepsin K in an in vitro assay of human osteoclastic resorption and an

in situ assay of osteoclast cathepsin activity. The potent selective cathepsin L inhibitors (Ki = 0.0099, 0.034, and 0.27 nM) were inactive in both the in situ cytochem. assay (IC50 > 1 μM) and the osteoclast-mediated bone resorption assay (IC50 > 300 nM). Conversely, the cathepsin K selective inhibitor was potently active in both the cytochem. (IC50 = 63 nM) and resorption (IC50 = 71 nM) assays. A recently reported dipeptide aldehyde with activity against cathepsins L (Ki = 0.052 nM) and K (Ki = 1.57 nM) was also active in both assays (IC50 = 110 and 115 nM, resp.) These data confirm that cathepsin K and not cathepsin L is the major protease responsible for human osteoclastic bone resorption.

IT **350796-38-2 350796-41-7**

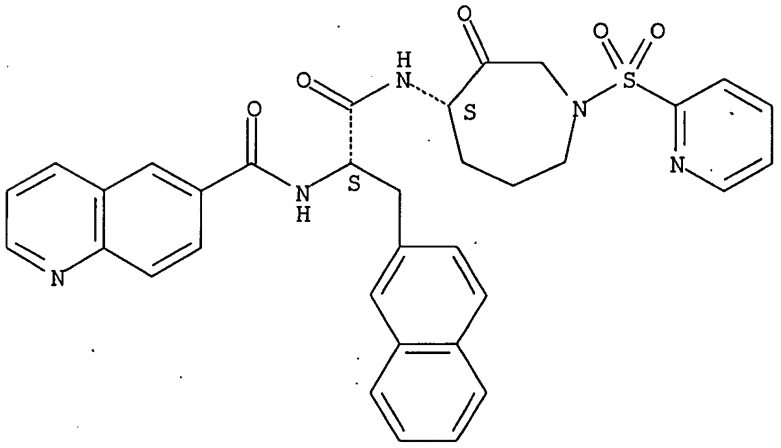
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)

(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)

RN 350796-38-2 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

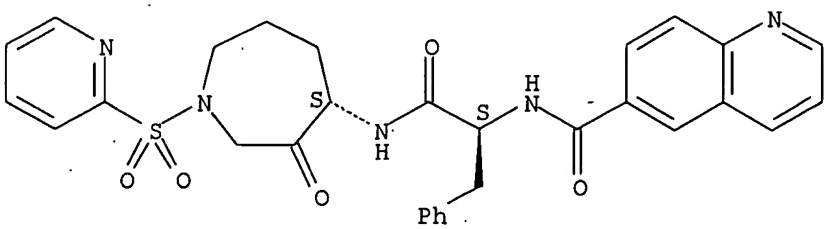
Absolute stereochemistry.



RN 350796-41-7 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

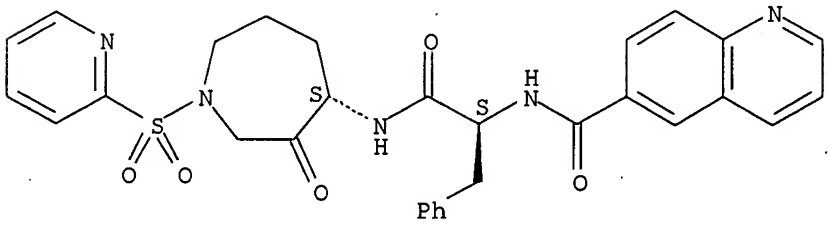


REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>

L1 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN
RN **350796-41-7** REGISTRY
ED Entered STN: 09 Aug 2001
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Quinoline-6-carboxylic acid [(1S)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]-2-phenylethyl]amide
CN SB 468433
FS STEREOSEARCH
MF C30 H29 N5 O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.

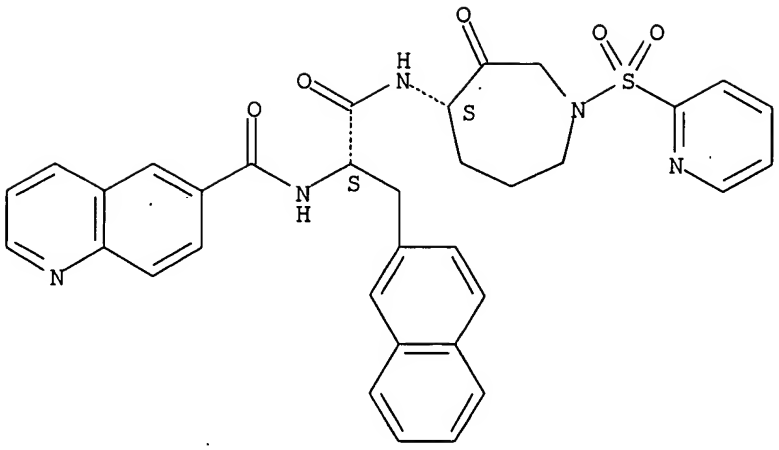


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L1 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2006 ACS on STN
RN **350796-38-2** REGISTRY
ED Entered STN: 09 Aug 2001
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Quinoline-6-carboxylic acid [(1S)-2-(naphthalen-2-yl)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]ethyl]amide
CN SB 468430
FS STEREOSEARCH
MF C34 H31 N5 O5 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



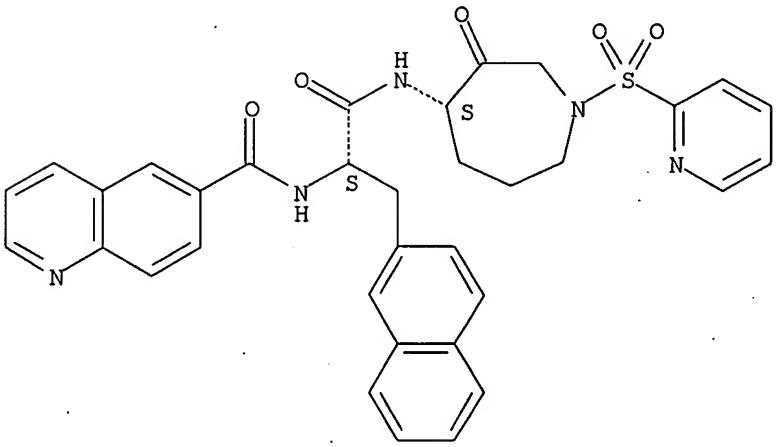
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

4 REFERENCES IN FILE CA (1907 TO DATE)
4 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=>

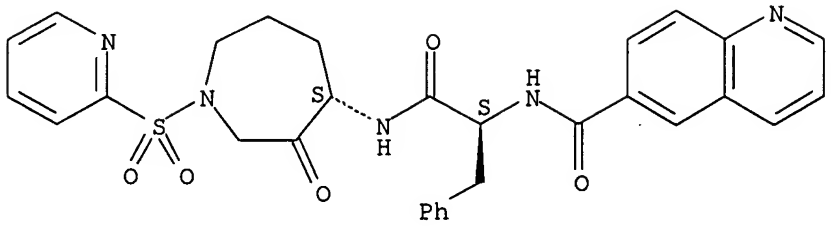
L4 ANSWER 1 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:665404 CAPLUS
DOCUMENT NUMBER: 141:103796
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro. [Erratum to document cited in CA135:120165]
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Hwang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2003), 278(34), 32484
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In Tables I and II, analogs **SB-468430** and **SB-468433** were originally reported to contain the quinoline-8-carboxamide moiety. Subsequent resynthesis revealed that in actuality these analogs contain the isomeric quinoline-6-carboxamide moiety. The modified structures are given in revised Tables I and II. Corrected Ki values for cathepsin L and cathepsin K in Table I are also given.
IT **350796-38-2, SB 468430 350796-41-7, SB 468433**
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro (Erratum))
RN 350796-38-2 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

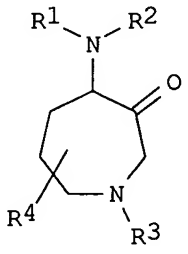
Absolute stereochemistry.



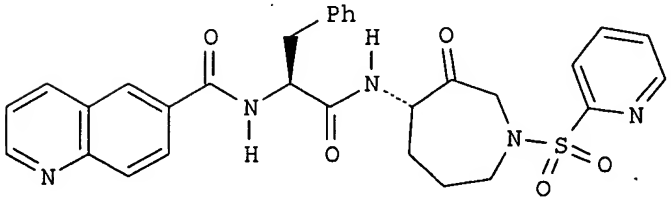
L4 ANSWER 2 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:803931 CAPLUS
DOCUMENT NUMBER: 141:295878
TITLE: Preparation of aminoazepanones as Cathepsin L inhibitors
INVENTOR(S): Marquis, Robert W.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 13 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004192674	A1	20040930	US 2004-772817		20040205
PRIORITY APPLN. INFO.:			US 2003-447558P	P	20030214

OTHER SOURCE(S): MARPAT 141:295878
GI



I



II

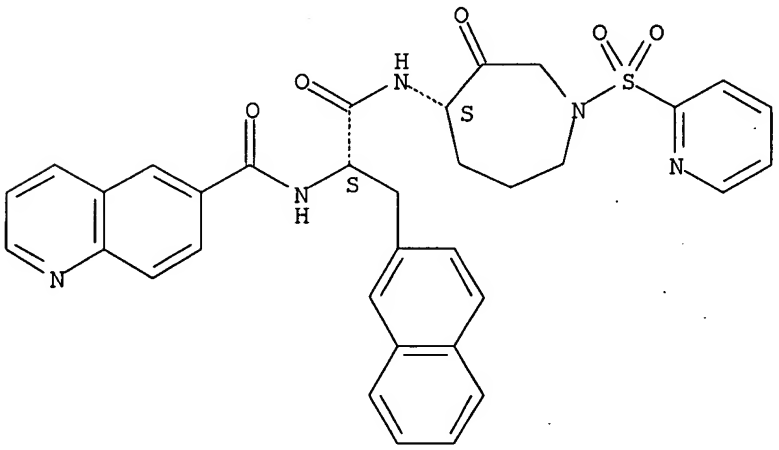
AB The title compds. I [R1 = substituted aminoalkylcarbonyl; R2 = H, alkyl, arylalkyl, etc.; R3 = H, alkyl, cycloalkyl, arylalkyl, etc.; R4 = H, alkyl, cycloalkyl, etc.] and their pharmaceutically acceptable salts are prepared and disclosed as inhibitors of Cathepsin L. Thus, e.g., II was prepared in a multistep synthesis employing N-Boc-phenylalanine. Consequently they are useful for preventing or treating diseases in which cathepsin L is implicated, such as rheumatoid arthritis or inhibition of

pos. selection of CD4 + T-cells by cortical thymic epithelial cells.

IT **350796-38-2P 350796-41-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of aminoazepanones as inhibitors of Cathepsin L)

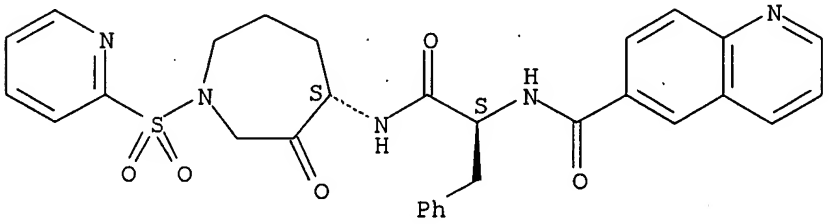
RN 350796-38-2 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN

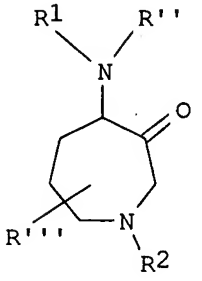
ACCESSION NUMBER:	2002:171694 CAPLUS
DOCUMENT NUMBER:	136:232208
TITLE:	Preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases
INVENTOR(S):	Tew, David G.; Thompson, Scott K.; Veber, Daniel F.
PATENT ASSIGNEE(S):	Smithkline Beecham Corporation, UK
SOURCE:	PCT Int. Appl., 220 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	4

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002017924	A1	20020307	WO 2001-US27178	20010831
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003144175	A1	20030731	US 2001-881334	20010614
AU 2001086983	A5	20020313	AU 2001-86983	20010831
EP 1320370	A1	20030625	EP 2001-966474	20010831
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004509083	T2	20040325	JP 2002-522897	20010831
PRIORITY APPLN. INFO.:			US 2000-653815	A2 20000901
			US 2001-881334	A2 20010614
			US 1998-113636P	P 19981223
			US 1999-164581P	P 19991110
			WO 1999-US30730	A2 19991221
			US 2000-593845	B2 20000614
			WO 2001-US27178	W 20010831

OTHER SOURCE(S): MARPAT 136:232208

GI



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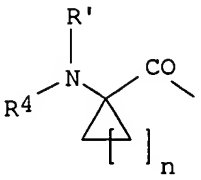


II

AB The present invention relates to methods of treating parasitic diseases which are mediated by cysteine proteases by administration of 4-aminoazepan-3-one protease inhibitors I (e.g. benzo[1,3]dioxole-5-carboxylic acid [(S)-1-(1-benzyl-3-oxoazepan-4-ylcarbamoyl)-3-methylbutyl]amide) and pharmaceutically acceptable salts, hydrates and solvates thereof. In particular, the present invention relates to a method of treating malaria by inhibiting the cysteine protease falcipain. Other diseases against which the claimed compds. are effective include trypanosomiasis (African sleeping sickness, Chagas disease), leishmaniasis, schistosomiasis, onchocerciasis (river blindness) and giardiasis. In I: R1 is R4NR'CHR3C(O)-, R5XCHR3C(O)-, R3CH2C(O)-, R4NR'CR''''R3C(O)-, II. R2 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R9C(O)-, R9C(S)-, R9SO2-, R9OC(O)-, R9R11NC(O)-, R9R11NC(S)-, R9(R11)NSO2-, 3-(2-pyridyl)benzylcarbonyl, 2-(3-(2-pyridyl)phenyl)ethyl, R7NR6CHR8Z-, and R9SO2R11NC(O)-. R3 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R3 and R' may be connected to form a

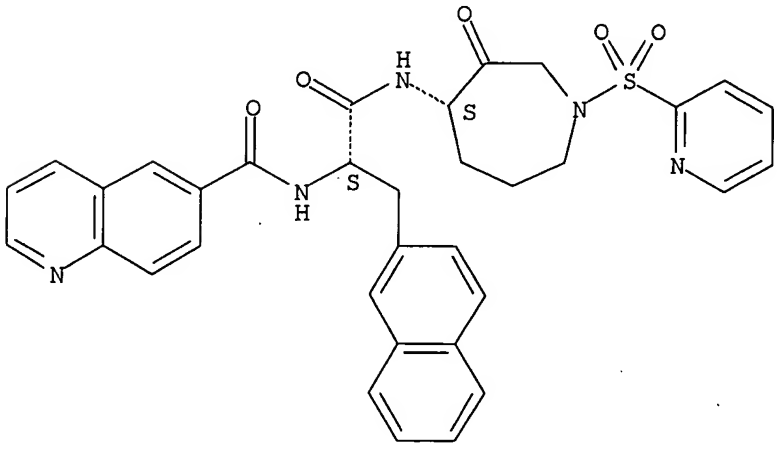
pyrrolidine, piperidine or morpholine ring. R4 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R5C(O)-, R5C(S)-, R5SO2-, R5OC(O)-, R5R12NC(O)-, and R5R12NC(S)-. R5 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R6 is H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R7 is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, Het-C0-6alkyl, R10C(O)-, R10C(S)-, R10SO2-, R10OC(O)-, R10R13NC(O)-, and R10R13NC(S)-. R8 is H, C1-6alkyl, C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. R9, R10 independently = C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl and Het-C0-6alkyl. R11, R12, R13, R', R'' independently = H, C1-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl. R''' is H, C1-6alkyl, C3-6cycloalkyl-C0-6alkyl, Ar-C0-6alkyl, and Het-C0-6alkyl; R'''' is C1-6alkyl, C3-6cycloalkyl-C0-6alkyl C2-6alkenyl, C2-6alkynyl, HetC0-6alkyl and ArC0-6alkyl. X is CH2, S, and O; Z is C(O) and CH2; n is 1-5. Although the methods of preparation are not claimed, 220 example prepns. are included.

IT **350796-38-2P**, Quinoline-6-carboxylic acid [(1S)-2-(naphthalen-2-yl)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]ethyl]amide **350796-41-7P**, Quinoline-6-carboxylic acid [(1S)-1-[[(4S)-3-oxo-1-(pyridin-2-ylsulfonyl)azepan-4-yl]carbamoyl]-2-phenylethyl]amide
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of 4-aminoazepan-3-one parasitic cysteine protease inhibitors effective against malaria and other diseases)

RN 350796-38-2 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



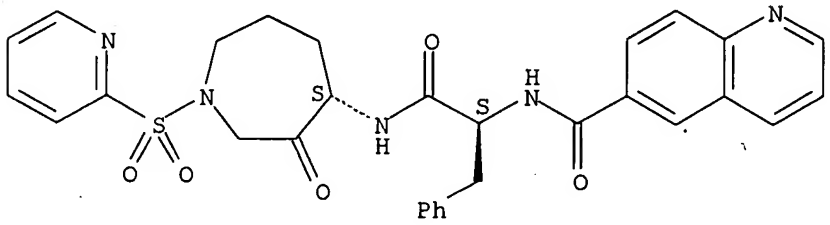
RN 350796-41-7 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

RN 350796-41-7 CAPLUS
CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:318582 CAPLUS
DOCUMENT NUMBER: 135:120165
TITLE: Potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro
AUTHOR(S): James, Ian E.; Marquis, Robert W.; Blake, Simon M.; Hwang, Shing Mei; Gress, Catherine J.; Ru, Yu; Zembryki, Denise; Yamashita, Dennis S.; McQueney, Michael S.; Tomaszek, Thaddeus A.; Oh, Hye-Ja; Gowen, Maxine; Veber, Daniel F.; Lark, Michael W.
CORPORATE SOURCE: Departments of Bone and Cartilage Biology, SmithKline Beecham Pharmaceuticals, King of Prussia, PA, 19406, USA
SOURCE: Journal of Biological Chemistry (2001), 276(15), 11507-11511
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cathepsins K and L are related cysteine proteases that have been proposed to play important roles in osteoclast-mediated bone resorption. To further examine the putative role of cathepsin L in bone resorption, we have evaluated selective and potent inhibitors of human cathepsin L and cathepsin K in an in vitro assay of human osteoclastic resorption and an in situ assay of osteoclast cathepsin activity. The potent selective cathepsin L inhibitors (Ki = 0.0099, 0.034, and 0.27 nM) were inactive in both the in situ cytochem. assay (IC50 > 1 μM) and the osteoclast-mediated bone resorption assay (IC50 > 300 nM). Conversely, the cathepsin K selective inhibitor was potently active in both the cytochem. (IC50 = 63 nM) and resorption (IC50 = 71 nM) assays. A recently reported dipeptide aldehyde with activity against cathepsins L (Ki = 0.052 nM) and K (Ki = 1.57 nM) was also active in both assays (IC50 = 110 and 115 nM, resp.) These data confirm that cathepsin K and not cathepsin L is the major protease responsible for human osteoclastic bone resorption.

IT Osteoclast
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)
IT Bone
(resorption; potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)
IT 60616-82-2, Cathepsin L 94716-09-3, Cathepsin K

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)

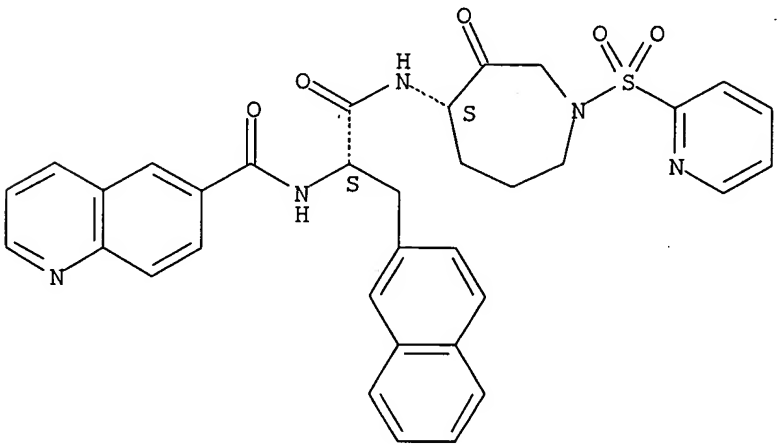
IT 167498-29-5, SB 412515 251457-34-8, SB 290190 **350796-38-2** 350796-39-3 **350796-41-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)

IT **350796-38-2 350796-41-7**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(potent and selective cathepsin L inhibitors do not inhibit human osteoclast resorption in vitro)

RN 350796-38-2 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-1-(2-naphthalenylmethyl)-2-oxoethyl]- (9CI) (CA INDEX NAME)

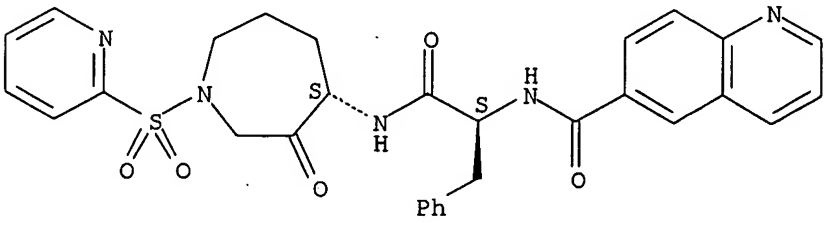
Absolute stereochemistry.



RN 350796-41-7 CAPLUS

CN 6-Quinolinecarboxamide, N-[(1S)-2-[[(4S)-hexahydro-3-oxo-1-(2-pyridinylsulfonyl)-1H-azepin-4-yl]amino]-2-oxo-1-(phenylmethyl)ethyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2003250069 EMBASE
TITLE: Osteoporosis: Challenges and new opportunities for therapy.
AUTHOR: Rotella D.P.
CORPORATE SOURCE: D.P. Rotella, Hopewell Discovery Chemistry, Bristol-Myers Squibb Company, PO Box 5400, Princeton, NJ 08543 5400, United States. david.rotella@bms.com
SOURCE: Current Opinion in Drug Discovery and Development, (2002) Vol. 5, No. 4, pp. 477-486. .
Refs: 55
ISSN: 1367-6733 CODEN: CODDFF
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Jul 2003
Last Updated on STN: 17 Jul 2003

AB Osteoporosis is a chronic disease that affects a large number of both men and women and is characterized by a decrease in bone mass, as well as weakened bones. It causes a significant amount of morbidity and mortality in patients and is often only diagnosed after a fracture occurs. This review will highlight recent advances in the development of novel anabolic approaches for treatment of osteoporosis, such as parathyroid hormone (PTH), calcium sensing receptor modulators, statins and prostanoid receptor agonists. Selected antiresorptive targets (cathepsin K inhibitors and vitronectin receptor antagonists) will also be surveyed.

L4 ANSWER 6 OF 7 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 2002172171 EMBASE
TITLE: Thiol-dependent enzymes and their inhibitors: A review.
AUTHOR: Leung-Toung R.; Li W.; Tam T.F.; Karimian K.
CORPORATE SOURCE: R. Leung-Toung, Medicinal Chemistry Department, Apotex Research Inc., 400 Ormont Drive, Toronto, Ont. M9L 1N9, Canada. rleung@apotex.ca
SOURCE: Current Medicinal Chemistry, (2002) Vol. 9, No. 9, pp. 979-1002. .
Refs: 190
ISSN: 0929-8673 CODEN: CMCHE7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 May 2002
Last Updated on STN: 30 May 2002

AB Biological thiol-dependent enzymes have recently received extensive attention in the literature because of their involvement in a variety of physiopathological conditions. The active thiol groups of these enzymes are derived from the cysteine residues present. Hence, in a biological system, the selective reversible or irreversible inhibition of the activity of these enzymes by modification of the thiol moiety may potentially lead to the development of a chemotherapeutic treatment. Despite all the research efforts involved in the attempt to develop potential chemotherapeutic treatments for the major diseases involving cysteine proteases, there are in fact no such treatments available yet. However, AG7088 (1) an inhibitor of rhinovirus-3C is in phase II/III

clinical trial for the treatment of common cold and VX-740 (2, pralnacasan) an inhibitor of caspase-1 is in phase II clinical trial as an anti-inflammatory agent for rheumatoid arthritis. Several other cysteine protease inhibitors (i.e., cathepsin K, and S) are in pre-clinical evaluation or pre-clinical development. Structure-based drug design approaches have been instrumental in the development of these inhibitors. Intensive biochemical studies on the cysteine proteases have shed some light on some potential targets for therapeutic development. In addition, new techniques and new ideas are constantly emerging. As such, an up-to-date review of the literature on thiol-dependent enzymes as potential targets and their inhibitors designed from peptidic, modified peptidomimetic scaffolds and from small heterocyclic molecules is presented.

L4 ANSWER 7 OF 7 EMBASE

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AB Inhibition of cysteine proteases is emerging as an important strategy for the treatment of a variety of human diseases. Intense efforts involving structure-based inhibitor design have been directed toward several cysteine proteases, including cathepsin K, calpain, human rhinovirus 3C protease and several parasitic cysteine protease targets. Other successful recent efforts have involved combinatorial synthesis and screening for identification of new inhibitor templates.

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